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(54) Title: USE OF A COMBINATION OF PENCICLOVIR AND ALPHA-INTERFERON IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF HEPATITIS B

(57) Abstract

The invention provides a method for the treatment or prophylaxis of hepatitis B virus infections in a human or animal patient which comprises administering to the patient effective or prophylactic amounts of penciclovir (or a bioprecursor thereof such as famciclovir) and alpha-interferon.

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USE OF A COMBINATION OF PENCICLOVIR AND ALPHA-INTERFERON IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF HEPATITIS B

The present invention relates to the use of a penciclovir or a bioprecusor therefor and alpha interferon in the treatment of hepatitis B virus infections and to pharmaceutical compositions containing the two compounds.

EP-A-271270 (Beecham Group p.l.c.) discloses the use of penciclovir or a pro-drug therefor and an interferon as a combined preparation for simultaneous, separate or sequential use in antiviral therapy, in particular in the treatment of herpesvirus infections.

EP-A-388049 (Beecham Group p.l.c.) discloses the use of penciclovir/famciclovir in the treatment of hepatitis B virus infection.

All references herein to penciclovir/famciclovir include pharmaceutically acceptable salts, such as the hydrochlorides, and solvates, such as hydrates.

It has now been discovered that penciclovir or its oral form, famciclovir, is particularly effective in treatment of Hepatitis B virus infections when administered in combination with alpha interferon.

Accordingly, the present invention provides a pharmaceutical product comprising a penciclovir or a bioprecusor therefor, such as famciclovir, and alpha interferon as a combined preparation for simultaneous, separate or sequential use in the treatment and/or prevention of hepatitis B virus infections.

The present invention also provides a method of treatment and/or prophylaxis of hepatitis B virus infections, which method comprises administering to a human or animal subject penciclovir or a bioprecusor therefor, such as famciclovir, and alpha interferon or a pharmaceutically acceptable salt or ester thereof.

The invention further provides the use of penciclovir or a bioprecusor therefor, such as famciclovir, in the manufacture of a medicament for administration in conjunction with alpha interferon for the treatment and/or prevention of hepatitis B virus infections.

Co-administration of penciclovir/famciclovir with alpha interferon is particularly useful for the treatment of prolonged hepatitis B virus infections.

Penciclovir/famciclovir and alpha interferon or a pharmaceutically acceptable salt or ester thereof may be administered as a single, pharmaceutical composition comprising effective amounts of the two active ingredients. Alternatively the two active ingredients may be co-administered in the form of two separate, pharmaceutical compositions for simultaneous or sequential use.

A usual dose of alpha interferon for use according to the invention is 3-10 MU (million units) three times per week.

Famciclovir or penciclovir may be given before, after, during or continued after cessation of interferon treatment or any combination of these.

The unit doses may be administered, for example, 1 to 4 times per day. The exact dose will depend on the route of administration and the severity of the condition being treated, and it will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient and immunocompromised patients may require an increased dosage.

When the two active ingredients are administered as separate preparations, they are preferably given enterally, such as orally or parenterally (e.g. intramuscularly or, more particularly, intravenously).

The dose of famciclovir administered may be 0.5 or 1 to 5 g per day, typically 1.5 g to 2.25 g per day.

According to a further aspect the invention provides a pharmaceutical composition, for use in human or veterinary medicine, which pharmaceutical composition comprises penciclovir or a bioprecusor therefor, such as famciclovir, and alpha interferon.

Compositions according to the invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients. Thus the compositions may, for example, be formulated for oral, buccal, parenteral or rectal administration. Compositions for administration by the oral route in the form of, for example, tablets or capsules are preferred.

Compositions for oral use such as tablets and capsules may be prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, micro -crystalline cellulose or calcium hydrogen phosphate); lubricant (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate) or wetting agent (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils) and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of one or both active ingredients.

For parenteral administration the compositions may be presented in a form suitable for bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in syringes, ampoules or in multi-dose containers with added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredients may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For rectal administration the compositions may be formulated as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The pharmaceutical compositions of the invention may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the penciclovir/famciclovir and the alpha interferon may be admixed together, if desired, with suitable excipients. Tablets may be prepared, for example, by direct compression of such a mixture. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Where the penciclovir/famciclovir and the alpha interferon are intended for administration as two separate compositions these may be presented in the form of, for example, a twin pack.

Examples of pharmaceutically acceptable salts are as described in the aforementioned patent references in the name of Beecham Group p.l.c. and references quoted therein, the subject matter of which is incorporated herein by reference.

It will be appreciated that the anti-hepatitis B virus nucleoside analogue and alpha interferon of this invention may be administered in combination with other pharmacologically active agents, in particular, other antivirals.

Example 1

Two patients suffering from chronic hepatitis B infection were studied. In each case, interferon (IFN) monotherapy had failed. However, both patients showed complete suppression of HBV-DNA during famciclovir therapy. As a relapse occurred (raised ALT, AST, HBV-DNA, HBe-Ag.+, positive histology) after stopping famciclovir monotherapy, a combination therapy was introduced. Famciclovir was administered 500-750mg tid. After a significant suppression of HBV-DNA was achieved, IFN was added in a dosage of 9-10 MU 3 times weekly for 6 months. During combination therapy liver function tests returned to normal and HBV-DNA became undetectable by hybridisation assay. One of the patients showed seroconversion from HBe-Ag to anti-HBe. Combination therapy was well tolerated with only interferon induced adverse events. In the patient with seroconversion a relapse was observed 8 months after the end of therapy with spontaneous recovery after 2 months. In the second patient famciclovir therapy was continued after stopping interferon, as seroconversion did not occur, although HBV-DNA remained undetectable by hybridisation. In conclusion, combination therapy was safe and well tolerated in both patients. (See H Hinrichsen et al., 48th AASLD, 7-11 November 1997, Chicago.)

Example 2

A R Marques et al. report (37th ICAAC, 28 September - 1 October 1997, Toronto) that the combination of famciclovir and interferon appears to be at least additive on suppressing HBV-DNA and resulted in the apparent clearance of HBe-Ag in two of five patients suffering from chronic hepatitis B, despite their prior failure on alpha-interferon alone.

Claims

1. A pharmaceutical product comprising a penciclovir or a bioprecursor therefor and alpha-interferon or a pharmaceutically acceptable salt or ester thereof as a combined preparation for simultaneous, separate or sequential use in the treatment or prophylaxis of hepatitis B infections.

2. A pharmaceutical product as claimed in claim 1, when said bioprecursor is famciclovir.

3. A method of treatment or prophylaxis of hepatitis B virus infections in a human or animal patient, which method comprises administering to the patient an effective or prophylactic amount of penciclovir or a bioprecursor thereof and alpha-interferon or a pharmaceutically acceptable salt or ester thereof.

4. A method as claimed in claim 3, wherein said alpha-interferon and penciclovir are administered simultaneously or sequentially.

5. A method as claimed in claim 3 or claim 4 wherein said bioprecursor is famciclovir.

6. A method as claimed in any of claims 3-5, wherein the dose of alpha-interferon is 3-10 MU/2-5 times per week.

7. A method as claimed in any of claims 3-6, wherein the dose of penciclovir is 0.5-5g/day.

8. A method as claimed in any of claims 3-7, wherein famciclovir or penciclovir is given before interferon treatment.

9. A method as claimed in any of claims 3-8, wherein famciclovir or penciclovir is given during interferon treatment.

10. A method as claimed in any of claims 3-9, wherein famciclovir or penciclovir is given after interferon treatment.

11. A method as claimed in claim 8 or 9, wherein famciclovir or penciclovir is continued after cessation of interferon treatment.

12. A method as claimed in any of claims 3-7, wherein famciclovir is given before and during interferon treatment.

13. A pharmaceutical composition for use in human or veterinary medicine, which pharmaceutical composition comprises penciclovir or a bioprecursor therefor and alpha-interferon or a pharmaceutically acceptable salt or ester thereof.

14. The use of penciclovir or a bioprecursor thereof in the manufacture of a medicament for the administration in conjunction with alpha-interferon or a pharmaceutically acceptable salt or ester thereof for the treatment or prophylaxis of hepatitis B virus infections.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/03236

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/21 //(A61K38/21,31:52)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 271 270 A (BEECHAM GROUP PLC) 15 June 1988 cited in the application * p.4, last par.; p.5, l.6-9, l.23-26; p.10; claims 1-10 * ---	1-14
X	DUSHEIKO G M: "NEW TREATMENTS FOR CHRONIC VIRAL HEPATITIS B AND C" BAILLIERES CLINICAL GASTROENTEROLOGY, vol. 10, no. 2, July 1996, pages 299-333, XP000610619 * p.305-306, Famciclovir; p.311, ultimate full par. * ---	1-14
X	EP 0 388 049 A (BEECHAM GROUP PLC) 19 September 1990 cited in the application * p.3, l.28-29, l.35-36; claims 1-8 * --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P,X	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US no.14113538, October 1997 MARQUES ET AL: " Combination therapy with famciclovir and interferon for the treatment of chronic hepatitis B" XP002059666 cited in the application see abstract & CHEMOTHERAPY, vol. 37, 1997, pages 219-20, -----	1-5,13, 14

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 97/03236

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